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10/532,663	12/05/2005	Robert Fuchs	0552-1016	8954

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EXAMINER
HIBBERT, CATHERINE S

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,663	FUCHS ET AL.	
	Examiner	Art Unit	
	Catherine S. Hibbert	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Amendment to the Claims filed 19 March 2008 is received and entered. Claims 1-3 are cancelled. Claims 4-24 are pending and under consideration in this action.

Response to Arguments

The rejection of cancelled Claims 1-3 under 35 U.S.C. 101 is moot.

The rejection of Claims 4-24 under 35 U.S.C. 112, second paragraph, is withdrawn based on Applicants Amendment to the Claims filed 19 March 2008. The rejection of cancelled Claims 1-3 is moot.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of Claims 4-6, 10-14, 16-18 and 21-22, under 35 U.S.C. 102(b) as being anticipated by Hinds et al in "Enhanced gene replacement in mycobacteria"

(Microbiology, 1999, Vol. 145: p. 519-527, entire document; of record) is maintained for reasons already of record and below.

Applicants arguments have been fully considered but are respectfully not found persuasive. Hinds et al teach the UV-irradiation of bacterial plasmid vector DNA in order to enhance subsequent homologous recombination in the mycobacteria. Hinds et al teach the inactivation of M. smegmatis genes and the use of a recombination assay to identify conditions (UV irradiation) in which homologous recombination is enhanced. Hinds et al teach the use of several different "suicide vectors" (p. 520, Table 1) and the use of reporter genes contained within and without the sequence of DNA intended targeted chromosomal insertion (see especially p. 522, Fig.1 and Fig. legend 1). Hinds et al teach the application of this method to gene replacement experiments in M. smegmatis, M. intracellulare, and M. tuberculosis (abstract). In addition, Hinds et al teach the use of single stranded phagemid DNA using the pSYCHOP construct (p. 524, ¶3, lines 1-3). Therefore, Hinds et al anticipates all the limitations of claims 4-6, 10-14, 16-18 and 21-22.

Applicants response is to traverse the rejection. Particularly, Applicants argument centers on the interpretation of independent Claim 4. For example, Applicant recites (pages 5-6 of Remarks):

> the method of the present invention as shown in independent claim 4 relates exclusively to methods in which the DNA vector molecule replicates in the prokaryotic or eukaryotic target cell prior to exposure to a mutagenic agent.

Applicants arguments have been fully considered but are respectfully not found persuasive because Applicants arguments are not commensurate with the scope of the claims, as written. For example, Applicants arguments are not commensurate with the scope of the claims because the instant Claim 4 recites: A method for *in vitro* insertion of a nucleic acid of interest initially included in a DNA vector, within a predetermined target nucleotide sequence present in a chromosome contained in a prokaryotic or eukaryotic cell, said method ***comprises:***

a) contacting the DNA vector comprising the nucleic acid of interest, and replicating said DNA vector in said prokaryotic or eukaryotic cell, with a mutagenic agent blocking the DNA replication in the cell;

b) transfecting said prokaryotic or eukaryotic cells with the DNA vector obtained at the end of step a); and

c) selecting prokaryotic or eukaryotic cells for which the nucleic acid of interest has been integrated into the predetermined target nucleotide sequence.

It is noted that claims must be given their broadest reasonable interpretation during examination. Accordingly, the broadest reasonable interpretation of the independent Claim 4 does not "relate exclusively to methods in which the DNA vector molecule replicates in the prokaryotic or eukaryotic target cell prior to exposure to a mutagenic agent". The open claim language "comprises" indicates that the method may have additional steps. In addition, step (c) is not required in any particular order with respect to steps (a) and (b). In addition, the method does not include a step of integration into

the chromosomal DNA. In addition, step (a), as written, does not require the DNA vector molecule replicates in the target cell prior to exposure to a mutagenic agent because the phrase "with a mutagenic agent blocking the DNA replication in the cell" appears to correlate to the contacting step (as the contacting step requires a phrase to indicate what is being contacted) which could occur before the replication step, as written. In addition, the steps of replicating and contacting of step (a) do not require a given order, as written.

Therefore, Claims 4-6, 10-14, 16-18, and 21-22 stand rejected under 35 U.S.C. 102(b) as being anticipated by Hinds et al for reasons already of record and above.

The rejection of Claims 4-5, 10-14, 16-19, 21 and 23 under 35 U.S.C. 102(b) as being anticipated by Ganiatsas et al in "SEK1 deficiency reveals mitogen-activated protein kinase cascade crossregulation and leads to abnormal hepatogenesis" (Proc. Natl. Acad. Sci. USA Vol. 95, pp. 6881–6886, June 1998, see whole document; of record) is maintained for reasons already of record and below.

Applicants arguments have been fully considered but are respectfully not found persuasive. Ganiatsas et al teach the use of the mutagenic agent (UV irradiation) in studies of homologous recombination using vectors containing reporter genes. Ganiatsas et al recite that "W9.5 ES cells were used for homologous recombination" and that "the targeting vector was produced by insertion of a 6-kb *Bgl*II fragment into the *Bam*HI site of pGKneo/TK followed by insertion of a 1-kb *Eco*RI fragment into the *Pme*I

site of the resulting vector". Ganiatsas et al further teach that the "Initial selection of targeted ES cells was carried out first in 175 mg/ml G418" (see whole document and especially Materials and Methods section lines 1-9). Therefore, Ganiatsas et al anticipates the limitations of claims 4-5, 10-14, 16-19, 21, and 23.

Applicants response is to traverse the rejection. Particularly, Applicants argument centers on the interpretation of independent Claim 4. For example, Applicant refers again to Remarks of pages 5-6:

> the method of the present invention as shown in independent claim 4 relates exclusively to methods in which the DNA vector molecule replicates in the prokaryotic or eukaryotic target cell prior to exposure to a mutagenic agent.

Applicants arguments have been fully considered but are respectfully not found persuasive because Applicants arguments are not commensurate with the scope of the claims, as written. For example, Applicants arguments are not commensurate with the scope of the claims because the instant Claim 4 recites: A method for *in vitro* insertion of a nucleic acid of interest initially included in a DNA vector, within a predetermined target nucleotide sequence present in a chromosome contained in a prokaryotic or eukaryotic cell, said method ***comprises:***

a) contacting the DNA vector comprising the nucleic acid of interest, and replicating said DNA vector in said prokaryotic or eukaryotic cell, with a mutagenic agent blocking the DNA replication in the cell;

b) transfecting said prokaryotic or eukaryotic cells with the DNA vector obtained at the end of step a); and

c) selecting prokaryotic or eukaryotic cells for which the nucleic acid of interest has been integrated into the predetermined target nucleotide sequence.

It is noted that claims must be given their broadest reasonable interpretation during examination. Accordingly, the broadest reasonable interpretation of the independent Claim 4 does not "relate exclusively to methods in which the DNA vector molecule replicates in the prokaryotic or eukaryotic target cell prior to exposure to a mutagenic agent". The open claim language "comprises" indicates that the method may have additional steps. In addition, step (c) is not required in any particular order with respect to steps (a) and (b). In addition, the method does not include a step of integration into the chromosomal DNA. In addition, step (a), as written, does not require the DNA vector molecule replicates in the target cell prior to exposure to a mutagenic agent because the phrase "with a mutagenic agent blocking the DNA replication in the cell" appears to correlate to the contacting step (as the contacting step requires a phrase to indicate what is being contacted) which could occur before the replication step, as written. In addition, the steps of replicating and contacting of step (a) do not require a given order, as written.

Therefore, Claims 4-5, 10-14, 16-19, 21 and 23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Ganiatsas et al for reasons already of record and above.

The rejection of Claims 4-21 and 23-24 under 35 U.S.C. 102(e) as being anticipated by Hoeijmakers et al in "Detection Methods Based on HR23 Protein Binding Molecules (US PGPub No:2003/0124605, filed 20 November 2002, which claims priority to Provisional Application No:60/331.773, filed 21 November 2001, see entire document; of record) is maintained for reasons already of record and below.

Applicants arguments have been fully considered but are respectfully not found persuasive. Hoeijmakers et al teach a method of targeted homologous recombination using vectors comprising identical 5'- and 3'- sequences respective to the target DNA contained in the chromosome (see especially Figure 1). Hoeijmakers et al teach the use of the mutagenic agents such as UV irradiation and 50 and 100uM concentrations of N-acetoxy-2-acetylaminofluorene (NS-AAF) (p.10, ¶ 132) and wherein the nucleic acid of interest encodes a protein of therapeutic interest, wherein an open reading frame is disrupted by a heterologous nucleotide sequence, and which codes an antisense RNA. For example, Hoeijmakers et al recite:

> An Ola129 mHR23A targeting construct was generated by converting the BglII site in exon II of clone pG7M23Ag1 (containing a 4 kb genomic EcoRI fragment subcloned in pGEM7) into a ClaI site, which (due to a ClaI site in the polylinker) allowed deletion of sequences downstream of the BglII site in exon II (clone pG7M23Ag7). Next, the remaining EcoRI site was removed by filling-in the overhangs with Klenow, resulting in clone pG7M23Ag9. After changing the BstXI site into a SalI site, the 3 kb XhoI-SalI fragment was cloned into SalI digested pGEM5, resulting in clone pG5M23Ag17. Next, the 3' arm of the construct, consisting of a Klenow-blunted 1.5 kb SmaI-XbaI fragment starting at the SmaI site in exon VII, was inserted in the blunted NdeI site of pG5M23Ag17 (giving pG5M23Ag20), followed by insertion of a Neo marker cassette in antisense orientation in the ClaI site (giving pG5M23Ag24). Finally, the NotI-NsiI insert of pG5M23Ag24 was recloned into a pGEM-9Zf(-) based vector containing a 2.8 kb thymidine kinase (TK) marker cassette (giving pG5M23Ag30).

In addition, Hoeijmakers et al teach that "cells stably expressing hXPC-GFP/hHR23B were rinsed with PBS, exposed to UV-C light (254 nm; Philips TUV lamp, dose as indicated in the text) and subsequently cultured at 37.degree. C. for various time periods (as indicated in the text). XPC was detected either by immunoblot analysis or by visualization in living cells using fluorescence microscopy. A similar approach was used to study the effect of N-acetoxy-2-acetylaminofluorene (NA-AAF, final concentration 50 or 100 μM)"(p.10, ¶ 132), and further teaches mouse and human (HeLa) cells (p.11, ¶ 136 and 141). Therefore, Hoeijmakers et al anticipates the limitations of claims 4-21 and 23-24.

Applicants response is to traverse the rejection. Particularly, Applicants argument centers on the interpretation of independent Claim 4. For example, Applicant refers again to Remarks of pages 5-6:

> the method of the present invention as shown in independent claim 4 relates exclusively to methods in which the DNA vector molecule replicates in the prokaryotic or eukaryotic target cell prior to exposure to a mutagenic agent.

Applicants arguments have been fully considered but are respectfully not found persuasive because Applicants arguments are not commensurate with the scope of the claims, as written. For example, Applicants arguments are not commensurate with the scope of the claims because the instant Claim 4 recites: A method for *in vitro* insertion of a nucleic acid of interest initially included in a DNA vector, within a predetermined

target nucleotide sequence present in a chromosome contained in a prokaryotic or eukaryotic cell, said method ***comprises:***

a) contacting the DNA vector comprising the nucleic acid of interest, and replicating said DNA vector in said prokaryotic or eukaryotic cell, with a mutagenic agent blocking the DNA replication in the cell;

b) transfecting said prokaryotic or eukaryotic cells with the DNA vector obtained at the end of step a); and

c) selecting prokaryotic or eukaryotic cells for which the nucleic acid of interest has been integrated into the predetermined target nucleotide sequence.

It is noted that claims must be given their broadest reasonable interpretation during examination. Accordingly, the broadest reasonable interpretation of the independent Claim 4 does not "relate exclusively to methods in which the DNA vector molecule replicates in the prokaryotic or eukaryotic target cell prior to exposure to a mutagenic agent". The open claim language "comprises" indicates that the method may have additional steps. In addition, step (c) is not required in any particular order with respect to steps (a) and (b). In addition, the method does not include a step of integration into the chromosomal DNA. In addition, step (a), as written, does not require the DNA vector molecule replicates in the target cell prior to exposure to a mutagenic agent because the phrase "with a mutagenic agent blocking the DNA replication in the cell" appears to correlate to the contacting step (as the contacting step requires a phrase to indicate what is being contacted) which could occur before the replication step, as

written. In addition, the steps of replicating and contacting of step (a) do not require a given order, as written.

Therefore Claims 4-21 and 23-24 stand rejected under 35 U.S.C. 102(e) as being anticipated by Hoeijmakers et al for reasons already of record and above.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine S. Hibbert, Ph.D., whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D., can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully submitted,

Catherine S. Hibbert
Examiner/AU1636

/David Guzo/
Primary Examiner
Art Unit 1636